

REMARKS

Applicants hereby request non-entry of the previously filed unentered amendments and request that the amendments above be entered.

After entry of this amendment, claims 1-15 are pending. The claims have been amended without prejudice or disclaimer and find support *inter alia* in the original claims. Claims 1 and 13 find further support in the specification, for example, at page 6, lines 28-32, and Example 8 at pages 32-36. No new matter has been added.

Applicants enclose herewith a Request for Continued Examination requesting entry of the above claim amendment and consideration of the present remarks. The above claim amendment and following remarks address the rejections in the Final Office Action dated April 27, 2010 and also the comments in the Advisory Action mailed August 31, 2010.

Claim Rejections – 35 U.S.C. § 103

Claims 1-11 and 13-15 remain rejected under 35 U.S.C. § 103(a) as being obvious over Wilms *et al.* (hereinafter Wilms”) in view of Moralejo *et al.* (hereinafter “Moralejo”). Applicants respectfully traverse the rejection for the reasons already of record. However, to expedite prosecution, the claims have been amended without prejudice or disclaimer to recite the claimed subject matter with more specificity. It is respectfully submitted that the present claims overcome the rejection for the reasons already of record and for the following additional reasons.

It is well established that under 35 U.S.C. § 103 the Examiner must consider the subject matter sought to be patented as a whole. See MPEP § 2141.02. As part of the “subject matter as a whole” consideration, “***a patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified.***” *In re Spinnoble*, 405 F.2d 578, 585, 160 USPQ 237, 243 (CCPA 1969) (emphasis added). Thus, where the inventor discovered a cause of problem and there was no teaching in the prior art which would suggest a solution for such a problem, the invention directing to solving that problem is nonobvious and thus patentable. *See id.*

It is noted initially that the amended claims now require the method for producing recombinant proteins in prokaryotic host cells by high-density cell fermentation in the presence of low concentration of L-rhamnose (i.e. from 0.01 g/l to 0.5 g/l). Similarly, the prokaryotic host

cell according to the present application is one that is capable of producing recombinant proteins under the control of an L-rhamnose-inducible promoter in high-density cell fermentation in the presence of low concentration of L-rhamnose (i.e. from 0.01 g/l to 0.5 g/l).

As discussed in Applicants' response dated January 20, 2010, Wilms shows that a concentration of L-rhamnose at about 2 g/L is needed for effective induction of an L-rhamnose-inducible promoter in protein production by high-cell-density fermentation. See Wilms at page 100, left Col., 2nd paragraph, and Figure 6. As demonstrated therein, low concentration of L-rhamnose (e.g., 0.5 g/L) was not sufficient for effective induction of the *rhaBAD* promoter in high-cell-density fermentation for protein production. Rather, a concentration of 2 g/L of L-rhamnose is reported to be optimal (and thus, required) for effective induction of the *rhaBAD* promoter for recombinant protein production in high-cell-density fermentation conditions. Nowhere in Wilms was additional effort attempted or suggested to lower down the need of L-rhamnose for effective induction of the *rhaBAD* promoter so to produce recombinant proteins more efficiently and economically by high-cell-density fermentation. In fact, neither Wilms nor the art recognized this problem until the present application (i.e. the concentration of L-rhamnose needed for effective induction is still high, see e.g., Specification at page 4, lines 12-26). By recognizing the cause of problem, Applicants searched and discovered a novel method that allows production of recombinant proteins in prokaryotic host cells under the control of a *rhaBAD* promoter in high-density cell fermentation conditions using only low concentration of L-rhamnose.

Because neither Wilms nor the art recognized the underlying problem that the present application intended to solve, one skilled in the art would not have been motivated to reach out to Moralejo and to make the modification as alleged by the Examiner to arrive to the subject matter of the present application. Accordingly, it is respectfully submitted that the claimed subject matter, as amended, when considered as a whole, is nonobvious over the prior art and thus patentable.

Moreover, Applicants note that, in maintaining the rejection, the Examiner again contends that given the teachings in the prior art and the level of skill, "it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention." Office Action at page 7. The

Examiner further argues that the positive teaching of a successful use of the *rhaB* gene mutants in Wilms would lead one skilled in the art to a reasonable expectation of using other known genes which performs a similar function. Office Action at pages 7-8. Applicants respectfully disagree.

It is well established that it is the Examiner's burden to establish *prima facie* obviousness and the reasonable expectation of success. "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

As discussed previously in Applicants' response dated December 22, 2008, *rhaB* and *rhaA* genes encode two enzymes with very different function and activity. Thus, the results obtained from using the *rhaB* gene mutants as reported in Wilms would not necessarily predicate what would be seen by using *rhaA* gene mutants, let alone the effect in reducing the concentration of L-rhamnose needed for effective induction of protein production. Simply stating that a skilled artisan would have had a reasonable expectation of success, without more, lacks the specificity required to support a legal conclusion of obviousness and thus, is insufficient to establish *prima facie* obviousness. Because a *prima facie* case of obviousness has not been established, the burden remains on the Examiner and Applicants should not be required to present any "evidence to the contrary" to rebut the unsupported finding of obviousness.

For at least the above reasons and for the reasons already of record, further in view of the present amendments, Applicants submit that Wilms and Moralejo, alone or in combination, do not render the present claims obvious. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claim 12 remains rejected under 35 U.S.C. §103(a) as being obvious over Wilms in view of Moralejo, and further in view of Israelsen *et al.* (hereinafter "Israelsen"). Applicants respectfully traverse.

As discussed above, the main claim as amended, when considered as a whole, is nonobvious and patentable over the cited Wilms and Moralejo. Because claim 12 depends from claim 1, the cited references, Wilms and Moralejo, further in view of Israelsen, would not render

claim 12 obvious for essentially the same reasons already of record and the additional reasons detailed above. Accordingly, reconsideration and withdrawal of this rejection is also respectfully requested.

CONCLUSION

For at least the above reasons, Applicants respectfully request withdrawal of the rejections and allowance of the claims. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the number given below.

Accompanying this response is a Request for Continued Examination and a petition for a two-month extension of time to respond to the Office Action mailed April 27, 2010 with the required fee authorization. No further fee is believed due. However, if any additional fee is due, the Director is hereby authorized to charge our Deposit Account No. 03-2775, under Order No. 12810-00091-US from which the undersigned is authorized to draw.

Respectfully submitted,

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